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TEMPORAL CHANGE IN RADIOSENSITIVITY OF MINIATURE SWINE AS EVALUATED BY THE SPLIT-DOSE TECHNIQUE

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FOREWORD
(Nontechnical summary)

Earlier studies using the split-dose technique with domestic swine revealed that these animals overrecovered from the effects of a sublethal dose of whole-body radiation. In most species studied by the split-dose technique, exposure to a conditioning dose of radiation which is two-thirds of the normal $LD_{50/30}$ will not result in mortality, but will cause subclinical permanent tissue damage. Doses of this magnitude (two-thirds of the normal $LD_{50/30}$) are at levels where a low level of mortality might be expected, however is rarely seen. Recovery may be complete, or partial if permanent damage has been done. The split-dose technique is based on the premise that if immediately after the conditioning dose the animals were given another radiation dose equal to the difference between the $LD_{50/30}$ and the conditioning dose, that 50 percent of the animals would succumb, and there would be no recovery at time zero.

A redetermined $LD_{50/30}$ can be calculated at various times (day or weeks) after the conditioning dose. This $LD_{50/30}$ measures the radiosensitivity of the animals after the prior irradiation and indicates the degree of recovery which has occurred.

In this study on miniature swine, the normal $LD_{50/30}$ was determined to be 237 rads. The present split-dose study showed the redetermined $LD_{50/30}$ dose, delivered 28 days after the 150-rad conditioning dose, to be 477 rads, significantly greater than the normal single-dose $LD_{50/30}$ of 237 rads. In terms of recovery, not only was there no evidence of residual injury from the initial 150 rads, but that additional radiation above and beyond the normal $LD_{50/30}$ dose was necessary to produce 50 percent lethality. This is interpreted as overrecovery or acquired radioresistance in these miniature swine and is arithmetically stated as 260 percent recovery.

ABSTRACT

Using the split-dose technique, recovery was measured in miniature swine exposed to whole-body ^{60}Co gamma radiation delivered at 34-35 rads/minute. The initial conditioning dose (150 rads) was approximately two-thirds of the normal $LD_{50/30}$ (237 rads). The redetermined or challenge $LD_{50/30}$ measured 28 days after the conditioning dose was 477 rads, indicating 260 percent recovery from the initial sublethal dose. Histopathological examinations of three animals euthanatized 28 days after 150 rads revealed no histologic evidence that could account for the radioresistant state at that time.

I. INTRODUCTION

The recovery pattern (extended overrecovery) of domestic swine following sublethal whole-body irradiation is unique among all species studied to date in that there is a dramatic overrecovery lasting for several months after a single exposure.[8,9,11,13] Study of this phenomenon is of prime importance in radiation biology in order that the mechanisms of response to divided or multiple exposure be better understood. Emergency occupational situations can exist, whether military or civilian, where multiple whole-body exposures may become necessary. More thorough understanding of recovery kinetics and permanent injury levels will permit more accurate hazard prediction schedules. Definition of the mechanisms responsible for overrecovery may illustrate better pharmacotherapeutic-radiotherapeutic combinations and schedules in the field of cancer therapy.

The most commonly used method to measure recovery is the split-dose technique. A group of animals are exposed to the first (conditioning) sublethal dose and subsequently exposed to the second (challenge) dose at a selected time following the conditioning dose. The animals are subdivided at the time of the challenge dose and given graded doses of sufficient range to permit calculation of a new or challenge $LD_{50/30}$. Comparison of this $LD_{50/30c}$* with a control single-dose $LD_{50/30}$ allows calculation of the degree of recovery.

II. PROCEDURE

One hundred and fourteen miniature swine were utilized in this study; 37 animals to determine the control, single-dose $LD_{50/30}$ and 77 animals in the split-dose or

* $LD_{50/30c}$ is used to distinguish the $LD_{50/30}$ of animals which received the initial conditioning dose from that of animals receiving single irradiation doses ($LD_{50/30}$)

redetermined $LD_{50/30c}$. Ten of these were of the Hormel strain, the remainder of the Pitman-Moore strain. All animals arrived via commercial aircraft and underwent a minimum of 4 weeks in quarantine prior to the study. During quarantine, all animals were examined, deparasitized and identified using the freeze-branding technique,[5] all under veterinary supervision. Animal holding facilities consisted of concrete-floored rooms, maintained under constant temperature conditions. The swine were divided nearly equally by sex (all being sexually intact) and housed 15 animals per room. All animals were at least 5 months of age at receipt, averaging 21.1 kg, and were sexually mature at initiation of the experiments. The animals were fed a custom-mixed dry meal, formulated for maintenance nutritional levels, thus permitting uniform growth rates with the option for selective feeding of smaller or larger animals.

After the exposure(s) the animals were returned to the same animal rooms and examined daily thereafter to observe any notable clinical changes or deaths.

Following quarantine and minimal holding times, usually 1 month after quarantine, the animals were exposed to whole-body ^{60}Co gamma radiation. The average body weight of the animals at this time was 29.0 kg. The animals were exposed one at a time, restrained in a wooden exposure box. All doses were delivered at 34-35 rads per minute, as measured at the midline of a tissue-equivalent phantom of the same dimensions as the thorax of typical miniature swine. The exposures were performed with the AFRRI ^{60}Co whole-body irradiator in the simultaneous bilateral mode of operation.[3] This configuration results in a Class A exposure, as defined in the International Commission on Radiological Units and Measurements Report 10e.[7] Miniature swine in these age-weight ranges are approximately 22 cm in width (at the widest portion of the thorax) and the midline tissue dose (MTD) deposition is 82 percent of that in air at the midpoint of the animal exposure volume.

Animal dose selections were based on swine mortality figures previously published.[1,2,4,8,12,14] For the split-dose $LD_{50/30c}$ study, the conditioning dose selected, 150 rads, was approximately two-thirds of the normal $LD_{50/30}$ and was sublethal. While 1-2 percent mortality might have been expected following 150 rads, there were no deaths within the 28-day period. This study is similar in design to that reported by Nachtwey et al.[8] All challenge doses were delivered 28 days after the initial or conditioning doses. A multistage dose selection design was used to select the second or challenge doses, wherein smaller groups of animals were exposed to doses over a wider range initially. Subsequent groups were used to fill in the number of animals per dose once the relationship of dose and mortality had been established.

Recovery from the sublethal conditioning dose was calculated according to the following equation:

$$\text{percent recovery} = \frac{D_2 - (D_1 - D_c)}{D_c} \times 100$$

where D_2 is the split-dose or redetermined $LD_{50/30c}$, D_1 is the normal $LD_{50/30}$ and D_c is the conditioning dose.

Eleven animals in the split-dose study were additionally used for quantitating bone marrow and peripheral blood responses. Two animals from each of the groups which received challenge doses of 250, 280, 320, 360, and 400 rads and one which received 450 rads were studied. Bone marrow aspirate samples were taken from the sternum using local anesthesia and aseptic technique at 48 hours then at weekly intervals following both the conditioning and challenge doses for approximately 3 months in survivors. Postirradiation differential and total nucleated cell counts were compared to preirradiation numbers, with each animal serving as its own control.

In addition, six animals in the normal $LD_{50/30}$ study had peripheral blood samples taken during the 30-day observation period following exposure. Blood samples were obtained by anterior vena cava venipuncture using disposable 10-ml syringes and either 18- or 21-gauge 1- to 1-1/2-inch needles. The animals were restrained in dorsal recumbency in a V-shaped trough with a metal bar holding the maxilla down. The complete blood counts (CBC) included: white blood count (WBC), red blood count (RBC), hemoglobin (Hb), hematocrit (Hct) and platelet count. All hematological analyses were performed using routine laboratory procedures.

Data were analyzed by routine statistical methods using either the AFRRI Scientific Data Systems computer or a Wang programmable electronic calculator. The data were analyzed using the probit method as outlined by Finney.[6]

Necropsies were performed on nonsurvivors and euthanatized survivors. Any gross lesions were noted and selected tissues taken for histopathological examination. In a separate experiment, three animals were given 150 rads, sampled twice weekly (peripheral blood and bone marrow) and euthanatized 28 days following the irradiation. Detailed necropsies were performed to evaluate all pertinent tissues and to note any significant lesions.

III. RESULTS

The normal $LD_{50/30}$ determined with 37 animals was 237 rads MTD (95 percent confidence limits 215-262). The mean survival time was 16.3 days, with a range of

11-24 days. This $LD_{50/30}$ is in agreement with other published studies dealing with high dose rate exposures of domestic swine[1,2,4,8,12] and pulsed gamma-neutron exposures of miniature swine;[14] see Table I. The current data are summarized in Table II.

The split-dose or redetermined $LD_{50/30c}$, carried out with 77 animals, was 477 rads MTD (95 percent confidence limits 402-566). The mean survival time was 17.9 days and ranged from 8 to 24 days. These data are summarized in Table III and Figure 1. As both sexes were included in the split-dose study, mortality was compared between males and females (Figure 1 and Table IV). Under these conditions,

Table I. Recent Radiation Lethality Studies with Swine

Radiation source	Type of exposure	Type of swine	Sex	Age (months)	Weight (kg)	Dose rate (rads/min)*	LD_{50} †	Reference
f n/γ	bilateral	domestic	NS‡	9-12	125-175	16.5 - 20	228	2
^{60}Co	multisource (bilateral)	domestic	♂ ♀	8	114	50	187	1
^{60}Co	multisource (bilateral)	domestic	♂ ♀	8	114	10	226	1
^{60}Co	4 π	domestic	♂ ♀	NS	34	17.5 - 28	210	4
^{60}Co	4 π	domestic	♂ ♀	NS	68	17.5 - 28	220	4
1 MVp x ray	bilateral	domestic	♀	8-9	108	8.7 - 9.6	262	8
^{60}Co	bilateral	domestic	♀	8	110	10.5	218	12
pulsed γ/n	unilateral	miniature	♂ ♀	6	34	prompt	218	14
^{60}Co	bilateral	miniature	♂ ♀	6-7	29	41.5 - 42.7	237	-

* Tissue dose in air
† Midline tissue dose in rads
‡ Not stated in reference

Table II. Dose Response and Mortality Data for Miniature Swine Following ^{60}Co Gamma Irradiation

Midline tissue dose (rads)	Mortality number dead/number exposed	Day of death postirradiation
180	0/5	
203	0/1	
220	4/7	16, 16, 21, 24
240	3/8	14, 15, 18
270	6/8	15, 16, 16, 17, 18, 18
330	7/7	11, 13, 13, 15, 16, 17, 17
400	1/1	16
$LD_{50/30}$ = 237 rads (215-262)*		mean survival time 16.3 days

* 95 percent confidence limits

Table III. Dose Response and Mortality Data for Miniature Swine: Redetermined $LD_{50/30c}$ 28 Days after 150 Rads

Challenge dose (rads)	Mortality number dead/number exposed	Day of death postirradiation
100	0/3	
250	0/7	
280	2/7	20, 24
320	1/11	17
360	3/10	17, 18, 19
400	4/10	15, 16, 16, 19
450	1/13	15
510	6/8	13, 16, 16, 19, 19, 24
600	7/8	8, 11, 18, 18, 19, 21, 23
$LD_{50/30}$ = 477 rads (402-566)*		mean survival time 17.9 days

* 95 percent confidence limits

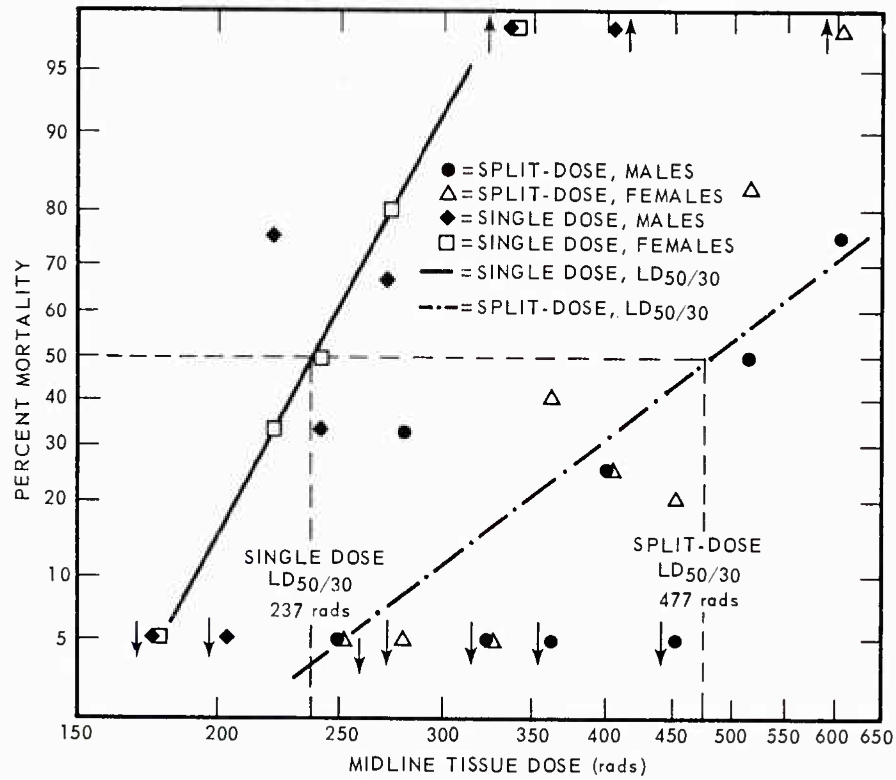

Figure 1. Dose response curves for miniature swine irradiated with ^{60}Co gamma radiation (plotted on normal probability x logarithmic coordinates). The arrows indicate points that are off scale at zero or 100 percent mortality.

the $LD_{50/30c}$ for females was 444 rads and for males was 609 rads. However, due to the relatively small number of animals in the study and the low number of mortality-producing dose groups, the confidence limits were correspondingly broad and the difference not statistically significant. It does appear that there could indeed be a sex difference in miniature swine radiosensitivity under the split-dose conditions, but it could be proven only with additional exposed animals. A similar sex-mortality

Table IV. Split-Dose Mortality Data Tabulated by Sex (150 Rads Conditioning Dose 28 Days Prior to Challenge)

Challenge dose (rads)	Females		Sex not recorded		Males	
	Survived	Died	Survived	Died	Survived	Died
100			3			
250	2		1		4	
280	3			1	2	1
320	6			1	4	
360	3	2		1	4	
400	3	1		2	3	1
450	4	1			8	
510	1	5			1	1
600		4			1	3
	$LD_{50/30}$ = 444 rads				$LD_{50/30}$ = 609 rads	

comparison made on the normal $LD_{50/30}$ data showed no difference in either slope or LD_{50} values. Earlier studies (single exposures) using mixed sexes of domestic swine did not show any differences in dose response by sex.[1,4,14]

The normal $LD_{50/30}$ and the split-dose $LD_{50/30c}$ are significantly different ($P < .01$), indicating that the radiosensitivity of miniature swine 28 days after the sublethal conditioning dose of 150 rads was changed dramatically from normal. In quantitative terms, the miniature swine had recovered 260 percent from the injury incurred from the initial sublethal dose.

The clinical syndrome of the animals succumbing from either single or double exposures was characterized by lethargy, anorexia and mild epistaxis in approximately one-third of the animals. Dehydration or diarrhea was not observed in any of the miniature swine.

The six animals in the normal $LD_{50/30}$ study which were bled for CBC's received doses between 203 and 240 rads. Three of the six animals died between 14 and 18 days after a 240-rad dose. The three survivors received doses of 203, 220, and 240 rads. Representative hematological data are summarized in Figure 2.

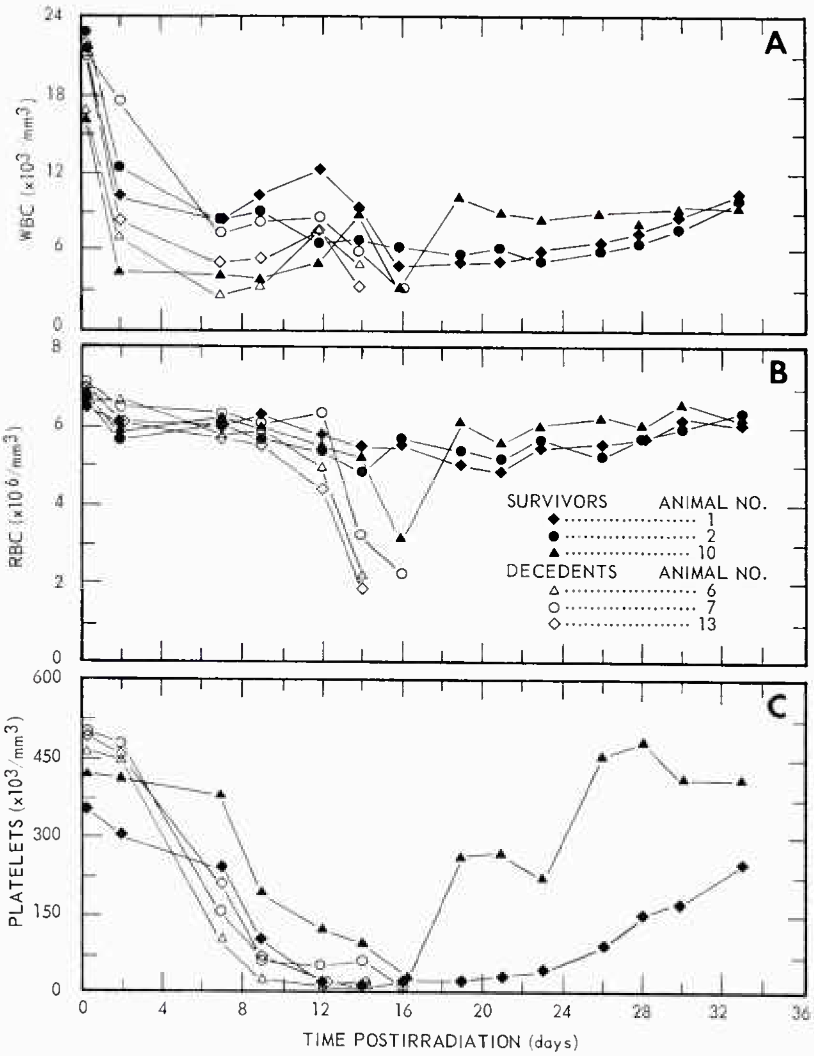

Figure 2. Selected hematological parameters for miniature swine exposed to single-dose midlethal ^{60}Co gamma radiation

Levels of erythrocytic parameters (RBC, Hb, Hct) for both the swine that lived and died remained essentially the same through day 12. Subsequently, erythrocytic values for those that died showed significant decreases at day 14 (2 hours prior to death for animal 13 and 24 hours prior to death for animal 6). Values of all three parameters for animal 7 continued to decline through day 16 with death occurring on day 18.

The erythrocytic parameters of the survivors showed gradual declines followed by gradual recovery over the 33-day sampling period. The values for one animal (10) dropped dramatically on day 16 but returned to normal levels by day 19.

The marked decline in erythrocytic parameters prior to death appeared to be a better indicator of impending lethality than were either leukocyte or platelet levels. The survivors' patterns then showed gradual returns toward base-line levels.

The response of the bone marrow cell renewal systems to irradiation was characterized by a pattern of early precipitous decline in absolute numbers of nucleated cells followed by variable degrees of cellular regeneration after both the conditioning and challenge doses. The levels of depression of nucleated marrow cells were invariably more severe following the challenge doses than after the smaller 150-rad conditioning dose given 28 days earlier. Only 10 to 20 percent of preirradiation cell numbers remained at the time of the nadir which occurred 2 to 7 days after the largest challenge doses. The marrow of most animals showed an initial onset of cellular regeneration within 2 weeks after irradiation, with nucleated cell values achieving variable percentages of their preirradiation numbers and ranging from partial to complete return to control levels by 28 days and 6 weeks after the conditioning and challenge doses, respectively. There was no consistent inverse relationship evident between the magnitude of the challenge dose and the degree of cellular regeneration eventually achieved during the approximately 3-month postchallenge period of study. Evidence that animals exposed to a challenge dose of 400 rads could recover their marrow cellularity equally as well as those exposed to 250 rads is indicated by the fairly typical pattern of response seen in Figure 3. Although there were temporary supranormal levels seen in absolute numbers of the most immature stages of the erythrocytic and granulocytic cell lines during the early intense regenerative periods following each of the two exposures, there was little evidence to suggest a sustained overproduction of nucleated cells by the bone marrow.

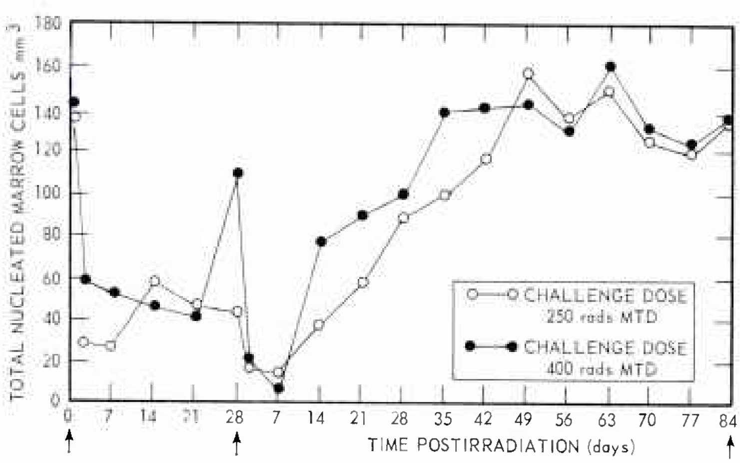

Figure 3. Pattern of depression and regeneration of total nucleated bone marrow cells/mm^3 in two miniature swine exposed to challenge doses of 250 rads and 400 rads 28 days following the 150-rad conditioning dose.

Gross pathological lesions noted at necropsy were consistent with those expected in deaths following midlethal irradiation. Pneumonia with pulmonary edema was the most striking lesion and was evident in half the animals. A few animals showed no gross visible lesions, but the majority had petechial and/or ecchymotic hemorrhages throughout all tissues. The degree of severity of lesions varied widely. The relationship between severity of lesions and radiation dose was most pronounced in the pneumonias, most of which were of bacterial origin. Pulmonary lesions varied from bronchopneumonia, serofibrinous pneumonia to fibrinohemorrhagic pneumonia as lethality increased from approximately 10 percent to 100 percent.

In necropsies and histopathological examinations performed on the three miniature swine euthanatized 28 days after 150 rads, no lesions were noted grossly and only minimal changes were evident microscopically. The lymph nodes showed minimal replacement fibrosis along with mild to moderate degrees of lymphoid hypoplasia. Livers showed a mild degree of chronic inflammation involving the interlobular connective tissue. Examination of bone marrow and other tissues revealed no histologic changes that were consistent with those which might be expected in the radioresistant state, i.e., intramedullary expansion of active hematopoietic tissue, extramedullary hematopoiesis or lymphoid hyperplasia.

IV. DISCUSSION

The phenomenon of overrecovery, as first reported in domestic swine by Nachtwey et al.,[8] has been demonstrated in miniature swine. Similar experimental designs were used, i.e., split-dose technique, conditioning dose of two-thirds of the normal $LD_{50/30}$, and high dose rate of high-energy photons. The present study measured recovery at day 28 only (challenge dose delivered 28 days after the conditioning dose), rather than measuring recovery at several time points after the conditioning dose, as noted in Figure 4. Under the conditions of this study, miniature swine showed an overrecovery of 260 percent at 28 days, a value comparable to that for domestic swine; Nachtwey et al.'s data indicated approximately 200 percent recovery on day 20.

As these studies involved dose levels within the range of doses producing deaths in the bone marrow syndrome, overrecovery has been thought to be a reflection of changes in hematopoietic kinetics. Very short periods of overrecovery have been observed in mice and sheep, but have been hypothesized to be the result of transient overshoots in the stem cell population during the overall process of hematopoietic

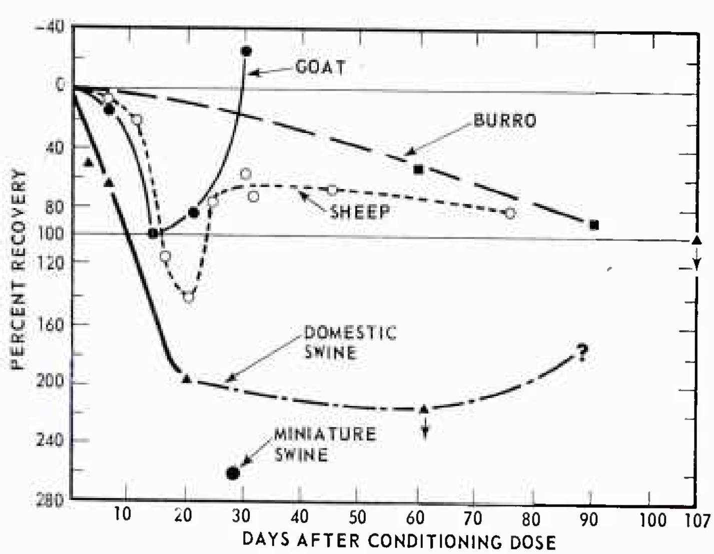

Figure 4. Interspecies comparison of recovery patterns after sublethal conditioning doses as evaluated by the split-dose technique

cellular repopulation.[10,11] Swine on the other hand show an overrecovery that is present between day 10 and day 107. It seems highly unlikely that a temporary overshoot in numbers of marrow stem cells could account for the extended period of resistance seen in swine. The thorough quantitative assessment made of the immature marrow cell stages distal to the microscopically unrecognizable stem cell pool in these miniature swine failed to detect evidence of sustained overproduction of immature marrow cells as would be expected from a concomitant increased pool size of their progenitor stem cells.

Complete gross and histopathological examinations at 28 days of the three animals which received only the 150-rad conditioning dose revealed no significant tissue changes that could be correlated with the radioresistant state. Little evidence of having previously received a sublethal dose of radiation remained. Routine peripheral hematological examinations failed to reveal any changes that would not have been predicted, based on responses shown by other sublethally irradiated mammals. The leukocyte responses were characterized by early depression with nadirs at 16 days and gradual returns toward normal, achieving approximately 50 percent of base-line level by 33 days. The platelet values of the survivors also had nadirs at 16 days with gradual returns toward normal values by the end of the observation period. Values of erythrocytic parameters showed only slight depression and generally remained within normal limits, with one exception at day 16.

Further studies of bone marrow cell kinetics coupled with detailed serum biochemical analyses will hopefully shed additional light on the physiological changes which are responsible for the marked radioresistance seen in swine in association with their recovery from prior sublethal irradiation.

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13. ABSTRACT

Using the split-dose technique, recovery was measured in miniature swine exposed to whole-body ^{60}Co gamma radiation delivered at 34-35 rads/minute. The initial conditioning dose (150 rads) was approximately two-thirds of the normal $LD_{50/30}$ (237 rads). The redetermined or challenge $LD_{50/30}$ measured 28 days after the conditioning dose was 477 rads, indicating 260 percent recovery from the initial sublethal dose. Histopathological examinations of three animals euthanatized 28 days after 150 rads revealed no histologic evidence that could account for the radioresistant state at that time.

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